AstraZeneca

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Date: MAY 24 2005

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2005 D-0103
Response to FDA Call for Comments
Guidance for Industry:
Using a Centralized IRB Review Process in Multicenter Clinical Trials

Dear Sir or Madam:

Reference is made to the March 2005 Federal Register notice announcing the request for comments on the Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials.

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Eileen Donovan, Sr. CQA Advisor at 302-886-4113.

Sincerely,

Gary M. Cooper
Director,
USRA, Regulatory Project Management
Telephone: 302-886-5132
Fax: 302-885-9186

GMC/ed
Enclosure

2005D-0103

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US Regulatory Affairs
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Guidance for Industry
Using a Centralized IRB Review Process in Multicenter Clinical Trials

General Comments

- **Comment 1**

  The apportionment of responsibilities between the centralized IRB and the institution's IRB should be very clear, as a lack of clarity with respect to responsibilities could result in longer delays in approval for those sites that will require review by the institution's IRB in addition to the central IRB review.

- **Comment 2**

  The primary model contemplated by this guidance is a centralized IRB review process developed for a multicenter trial, denoting that an institution may apportion IRB review responsibilities between a central and its own IRB; however, it fails to suggest a method of conflict resolution when a central and an institution's IRB disagree with respect to the review process.

  There is a concern that the apportionment of responsibilities between a central IRB and an institution's IRB will add additional complexity, expense, and delay to an already challenging review process.

  Illustrations of various complexities that apportionment of responsibilities may add to the review process are set forth below.

  1. Will the central IRB be responsible for reviewing Investigator Safety Letters (expedited SAE reports)?
  2. Will the central IRB be responsible for reviewing SAEs or pre-specified adverse events for patients? The institution's IRB usually has a set of rules that guides the reporting of SAEs experienced by research subjects at the site.
  3. Will the central IRB review and track the receipt of a study closeout letters, summarizing the number of research subjects enrolled, withdrawn, etc. and documentation that all study case report forms have been forwarded to the sponsor by each study site?
  4. Will the central IRB be responsible for the annual renewal of the study? Will the central IRB specify the application process for the sites for the annual renewal (renewal application, automatic review, study summary submitted) etc?
  5. Will the central IRB require submission of periodic safety summaries by the sponsor?

- **Comment 3**

  It is crucial that the central IRB be familiar with the local communities and has a working knowledge of the applicable local laws, regulations, and local attitudes toward research activities. Further, the central IRB minutes should document how relevant community issues and other local factors, including applicable local law and regulations were considered in the review.

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Section	**Page or Line Number**	**Comment or proposed replacement text**
II	74-77	The guidance states that, " A site may rely entirely on the central IRB for initial and continuing review of a clinical trial, or it may rely primarily on the central IRB, but use the IRB with which it is affiliated for certain aspects of the review (e.g., review of informed consent for local concerns). Can this be done efficiently? Important to the success of apportionment will be that there is a clearly documented written agreement and approval of the review procedures.
III	101-103	If the sponsor can initiate plans for the use of the central IRB, the sponsor should also have the flexibility to facilitate the review of protocol amendments, ICFs, and other documents with the central IRB. The guidance provides that sponsors can initiate plans and facilitate agreements " and other necessary communications among the parties involved." Arguably, this could include the ability to facilitate review of protocol amendments, ICFs, etc. *Suggested addition to the wording: " Sponsors can also initiate plans for use of a centralized IRB review process and facilitate agreements and ongoing activities of sponsored trials with respect to protocol amendments, revisions of informed consent documents and any other documents that require IRB review and approval during the course of the trial as well as other necessary communications among the parties involved."
III and IV	92-92 119-120 151-156	How feasible is it for a centralized IRB to collect, maintain, interpret and use information from an institution's IRBs from across the USA?
IV	151-152	There should be documentation that the individuals who are providing information to the central IRB are qualified to do so. That is, they are familiar with the local community and have knowledge of the applicable local laws/regulations. The qualifications of such persons or organizations should be clearly documented and include more than a simple attestation or certification. It should outline, using factual information, how and why the individual is qualified.

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		This is especially important in areas where there is an indigent population or otherwise vulnerable population (e.g., homeless, religiously inclined to certain attitudes, elderly etc.). * Suggested addition to the wording: " Provision of relevant local information to the central IRB in writing by individuals or organizations familiar with the local community, laws, and regulations, institution, and clinical research. The central IRB shall obtain documentation that the individuals or organizations providing the information are qualified to do so. The document should list the qualifications of the individual, not be just a signature attesting that the individual is qualified. The central IRB shall retain said documentation.
IV	155-156	Suggest that the limited review need not be a full membership review, but could be an ad hoc expedited review by an IRB member who is designated to do so by the Chairperson to the IRB. *Suggest addition to the wording: "Limited review of a central IRB-reviewed study by the institution's own IRB, with that limited review focusing on issues that are of concern to the local community. The review need not be a full membership review; and ad hoc expedited review by an IRB member designated by the IRB Chairperson is acceptable."
IV	157-158	It should be clarified that "relevant community issues" includes consideration of local laws/regulations. *Suggested addition to the wording: " Other mechanisms may also be appropriate. IRB meeting minutes or other records should document how relevant community issues and local laws/regulations were considered in the review."
IV		The guidance should also include the evaluation of the investigator as part of its assessment of local aspects of the review. The IRB should not simply approve the protocol without assessing the professional qualifications. Competence and past practices of the investigator in some way, e.g., obtaining curriculum vitae and license.
V	171-174	Should clarify whether the written agreements between the central IRBs and IRB of the participating institution have to be in place before the study protocol can be reviewed and approved by the central IRB.
VI	198-199	In line with Section V (lines 170-177) the institution's IRB should document how it implements its responsibilities under the agreement. *Suggested addition to the wording: " For agreements that apportion IRB review responsibilities between a central IRB and an institution's IRB, we recommend that the institution's IRB have written procedures describing and documenting how it implements it's

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		responsibilities under the agreement."
VIII		Include more examples of Cooperative IRB Review Models.